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10/525,679	02/17/2005	Hae-Young Suh	DE1617	3749

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EXAMINER	
MONTANARI, DAVID A	

ART UNIT	PAPER NUMBER
1632	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/525,679	SUH ET AL.	
	Examiner	Art Unit	
	David Montanari	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *28 April 2009*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-14* is/are pending in the application.

4a) Of the above claim(s) *9-14* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-6 and 8* is/are rejected.

7)☒ Claim(s) *7* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *4/28/2009*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. Applicants arguments filed on 4/28/2009 have been considered but are not found persuasive.

2. Claims 1-8 are examined in the instant application.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1, 2, 5 and 6 remain rejected under 35 U.S.C. 103(a) as being unpatentable over Woodbury et al. (2000, J. Neuroscience Res., Vol. 61, pgs. 364-370) and Guillemot F. (1999, Experimental Cell Res., Vol. 253, pgs. 357-364) for reasons of record in the Non-Final office action mailed on 12/29/2008 and repeated below.

The specification teaches on pg. 1 line 13 that "Mesenchymal stem cells (MSC) are multipotent bone marrow stromal cells aiding hematopoiesis". For the purposes of this rejection, the bone marrow stromal cells that are differentiated into neuronal cells taught in the art below are applicable over the claimed MSC's of the invention.

Woodbury et al. teach that human bone marrow stromal cells (MSC) have the capacity to differentiate into neurons (pg. 364, Abstract). Woodbury continues to teach that human MSC neuronal induction was carried out by culturing said cells in media comprising DMEM, 1-10 mM of BME (pg. 365 col. 1 parag. 1) and 10 μM of forskolin (pg. 365 col. 1 parag. 5 last sentence). Woodbury concludes by teaching they are the first to report that peripheral

mesenchymal stem cells can differentiate into neurons in vitro and that MSC's may be useful in the treatment of a wide variety of neurologic diseases (pg. 369 col. 1 parag. 2). Woodbury does not teach a method of transdifferentiating MSC into neuronal cells using bHLH transcription factors.

However, at the time of filing it was known in the art that bHLH transcription factors played a significant role in the determination of neuronal fates in cells. Guillemot F. teaches that "proteins of the bHLH class have central role in the determination of neuronal lineages in the peripheral and central nervous system and in the acquisition of pan-neuronal traits by differentiating neurons" (pg. 357 col. 1 parag. 1 lines 6-11). Guillemot continues to teach that a large number of transcription factors are sequentially and transiently expressed in neural precursor cells as neurogenesis proceeds and that the bHLH class of transcription factors play a important role in cell-type specification (pg. 357 col. 1 parag. 1 lines 1-3 and col. 1 last two lines bridge col. 2 parag. 1). Guillemot continues that a variety of bHLH genes such as neurogenin, MASH1, MATH3, neuroD and neuroD2 are expressed in a wide variety of cells that will commit to a neural lineage (pg. 357 col. 2 last sentence bridge pg. 358 col. 1 parag. 1 and Fig. 1). Guillemot concludes that "by controlling the ability of neural progenitors to respond to extrinsic factors, bHLH proteins may play an important role in integrating signals from the environment into transcriptional programs of differentiation" (pg. 361 col. 2 parag. 1 last sentence).

Thus it would have been prima facie obvious to ordinary artisan at the time of filing to combine the teachings of Woodbury teaching that MSC have the capacity to differentiate into neurons and that they would be useful for the treatment of a variety of neurological diseases with the teachings of Guillemont teaching that bHLH transcription factors have a central role in

determining neuronal cell differentiation to transdifferentiate MSC into neuronal cells by increasing a bHLH transcription factor in a MSC. Additional motivation is provided by Guillemont in teaching a variety of bHLH transcription factors including neurogenin, MATH3 and MASH1.

Thus the cited art clearly provides a case of prima facie obviousness.

Response to Arguments

Applicants Arguments

Applicants argue in amendment filed on 4/28/2009 that although Woodbury et al. discloses that cultured BMSCs exhibited a neuronal phenotype by expressing neuron-specific enolase, NeuN, neurofilament-M and tau, recent studies have indicated that the identification of such proteins is not sufficient or might be even incorrect to confirm the differentiation into neural cells. Applicants continue that Guillemot merely discloses a role of a bHLH transcription factor in differentiation of neuronal progenitor cells, not MSCs, into neuronal cells and does not teach or suggest transdifferentiation of MSCs, whose developmental lineage is totally different from that of neuronal progenitors, into neurons.

Applicants continue that although bHLH proteins were known in the art by Guillemot, the technical idea that bHLH transcription factors are employed to transdifferentiate MSCs into neuronal cells was not known at the time of filing of the subject application. Further, Applicants argue, since none of the cited references teach or suggest the critical technical feature of the subject invention, i.e., the use of bHLH transcription factors for transdifferentiating the MSCs into neuronal cells, those skilled in the art would have no basis for using the combination of the cited references as suggested by the Examiner, without the aid of hindsight.

Applicants continue to argue that recent studies have found that the method of identifying the differentiation of BMSCs into neuron-like cells employed in Woodbury et al. is not sufficient or may be even incorrect to confirm the differentiation of MSCs into neuronal cells since morphological change into neuron-like morphology and increases in immunolabeling for certain neuronal markers such as NSE and NeuN are not the result of genuine neuronal differentiation but represent cellular responses to chemical stress *(see the* Abstract, in Exhibit 1 attached to applicants response filed September 9, 2008, on page 185, and note that Exhibit 1 directly cites Woodbury et al. on page 175, left column, 3rd line and in the Results).

Applicants continue to argue that the Abstract of Neuhuber et al. in Exhibit 5, attached to applicants response filed September 9, 2008, reported that "a dissection of molecular signaling and commitment events may be necessary to verify the ability of MSC transdifferentiation to neuronal lineages," while mentioning Woodbury et al. as one of the in vitro differentiation protocols leading to unexpected, misleading results. Applicants continue that it cannot be said that MSCs were differentiated into neuronal cells without demonstrating electrophysiological properties of differentiated MSCs. Applicants continue that the subject invention has demonstrated that MSCs expressing bHLH transcription factor not only express neuron-specific proteins but also have electrophysiological properties *(see* Example 4, page 10 of the subject specification).

Applicants continue that in a developmental process, neuronal precursor cells or neuronal stem cells, which are committed to be differentiated into a neuron, are derived from ectoderm, while MSCs, which are committed to be differentiated into bone cells, cartilage cells and the like, are derived from mesoderm. Applicants continue, therefore, the differentiation potential of

MSCs is quite different from that of neuronal progenitor cells or neuronal stem cells. Applicants conclude that it is not obvious to transdifferentiate MSCs, which have an embryologically different differentiation potential as compared with neuronal precursor cells or neuronal stem cells, into neuronal cells by expressing therein a certain bHLH transcription factor. Applicants continue that this teaching is also supported by Paul Lu et al. in Exhibit No. 4, attached to applicants response filed September 9, 2008, describing that 'transdifferentiation' is a rare phenomenon and is not readily explainable in terms of normal developmental process *(see* page 175, right column, second paragraph). An IDS is attached hereto to make of record the Exhibits 1-5 as attached to applicants response filed September 9, 2008. These arguments are not persuasive.

Response

While Applicant has argued that there is a potential scientific basis that the bone marrow stromal cells taught in the art above cannot turn into neurons, this argument does not overcome the rejection of record. The rejection of record has established a series of facts: 1) that mesenchymal stem cells (MSCs) are multipotent bone marrow stromal cells (specification pg. 1 lines 13-16), 2) that bone marrow stromal cells exhibit multiple traits of a stem cell population and can be differentiated into neurons (Woodbury et al., Abstract) and 3) that bHLH transcription factors have a significant role neuronal cell differentiation (Guillemot et al.). Further attached with this action is a definition provided by medterms.com which defines transdifferentiation as "**1.** The change of a cell or tissue from one differentiated state to another. **2.** The differentiation of a tissue-specific stem cell into another type of cell as, for example, a

bone marrow stem cell differentiating into a neuron." The instant specification provides no definition for the term "transdifferentiation".

The invention as claimed requires only one step, transdifferentiating MSCs into neuronal cells by increasing the level of a bHLH transcription factor in the MSC. Woodbury teaches that bone marrow stromal cells, which are MSCs, can be differentiated into neurons and Guillemont teaches that bHLH transcription factors play a significant role in differentiating cells into a variety of neuronal phenotypes. Applicants arguments regarding the studies and teachings by Neuhuber and Lu pertaining to genuine neuronal differentiation are also not persuasive since each of these teachings are assumptions based upon observations and have not established that bone marrow stromal cells cannot in fact transdifferentiate into neuronal cells in view of the evidence and teachings provided in the art cited above. The rejection above requires motivation at the time of filing to arrive at the claimed invention. At the time of filing it was taught and demonstrated in the art that bone marrow stromal cells can differentiate into neuronal cells and that bHLH transcription factors are significantly involved in the determination of neuronal fate during cell differentiation. The ordinary artisan based upon these teachings would arrive, based upon prima facie obviousness, at the claimed invention of transdifferentiating MSCs into neuronal cells comprising increasing the level of a bHLH transcription factor in the MSC. The definition provided for the term "transdifferentiation" further supports the fact transdifferentiation of bone marrow stromal cells is actually occurring when the teachings of Woodbury and Guillemont are combined. At the time of filing the ordinary artisan is provided with the teaching and motivations that bone marrow stomal cells (MSCs) have the capacity to differentiate into neuronal cells and further Woodbury teachings examples of how to differentiate

bone marrow stomal cells into neuronal cells. Further at the time of filing, the ordinary artisan is provided teachings and motivations by Guillemont that bHLH transcription factors play a significant role in the determination of neuronal fates in cells and more specifically teaches that that a variety of bHLH genes such as neurogenin, MASH1, MATH3, neuroD and neuroD2 are expressed in a wide variety of cells that will commit to a neural lineage. These bHLH transcription factors are expressed before a cell commits to a neural lineage and provide the ordinary artisan a reasonable expectation of success that their expression in a cell would influence the cells differentiation towards a neuronal type. While the bone marrow stromal cells taught by Woodbury are taught as having neuronal potential, this is same for the cells recited in the claims, mesenchymal stem cells. Mesenchymal stem cells are of stromal origin and are not neuronal before differentiation, but will remain stromal unless differentiated, just as the bone marrow stromal cells taught by Woodbury. Since neither mesenchymal stem cells nor bone marrow stromal cells are neuronal in their undifferentiated stromal state, the ordinary artisan would reasonably conclude that they are both, based upon their neuronal differentiation potential, considered neural progenitors.

Applicant's arguments regarding the differentiating potential of bone marrow stromal cells are also not persuasive. Bone marrow stromal cells have the capacity to differentiate into a variety of cell types, including neuronal types as evidenced by the teachings of Woodbury. The art has demonstrated that bone marrow stromal cells have the potential to differentiate into neurons. There is nothing non-obvious or unexpected about adding a neuronal promoting factor to cells already demonstrated to differentiate into neurons. Further post-filing art has clearly demonstrated that bone marrow stromal cells can in fact be induced to become neural progenitor

cells by increasing intracellular cAMP (see Abstract of U.S. Patent 7,547,545, Prockop et al.). Based upon the teachings provided by Prockop et al., the neural progenitor properties of bone marrow stromal cells would be an inherent property. Prockop et al. did not differentiate bone marrow stromal cells, but rather increased endogenous levels of cAMP to induce said cells to become neural progenitors (col. 2 lines 26-35). Thus for the reasons above and of record the rejection is maintained.

Claims 3 and 4 remain rejected under 35 U.S.C. 103(a) as being unpatentable over Woodbury et al. (2000, J. Neuroscience Res., Vol. 61, pgs. 364-370) and Guillemot F. (1999, Experimental Cell Res., Vol. 253, pgs. 357-364) as applied to claims 1, 2, 5 and 6 above, and further in view of Elwood et al. (1998, Blood, Vol. 91, pgs. 3756-3765) for reasons of record in the Non-Final office action mailed on 12/29/2008 and repeated below.

Woodbury and Guillemot combined teach a method of using bHLH transcription factors to transdifferentiate MSC. Woodbury and Guillemot do not teach a method of transducing MSC with a viral vector coding for a bHLH transcription factor.

However at the time of filing it was known in the art that it was routine to use viral vectors to transduce cells. Ellwood et al. teaches that the product of the SCL gene is a bHLH transcription factor that is essential for the development of hematopoietic stem cells (pg. 3756, Abstract). Ellwood continues to teach that in order to force expression of SCL in CD34+ cells isolated from human bone marrow, an SCL retrovirus was used to transduce said cells (pg. 3756, Abstract and pg. 3760, col. 2, parag. 2, 2nd to last sentence).

Thus it would have been prima facie obvious to the ordinary artisan at the time of filing to combine the teachings of Ellwood regarding the utility of using retroviral vectors to transduce cells with a bHLH transcription factor with the teachings of Woodbury and Guillemont regarding a method of transdifferentiating MSC into neuronal cells to transduce a bHLH transcription factor in a viral vector into a MSC to transdifferentiate said MSC into a neuronal cell.

Thus the cited art clearly provides a case of prima facie obviousness.

Response to Arguments

Applicants Arguments

Applicants argue that the rejection of claims 3 and 4 is traversed for the same reasons set forth in the rejection of claims 1, 2, 5 and 6. Applicants continue that further Ellwood does not teach or suggest the method of claim 1 nor claims 2, 5, and 6 in combination with Woodbury and Guillemot. These arguments are not persuasive.

Response

As discussed above the rejection is maintained and further Applicant has not indicated any particular arguments or deficiencies in the Ellwood reference concerning its use in the pending rejection.

Claim 8 remains rejected under 35 U.S.C. 103(a) as being unpatentable over Woodbury et al. (2000, J. Neuroscience Res., Vol. 61, pgs. 364-370) and Guillemot F. (1999, Experimental Cell Res., Vol. 253, pgs. 357-364) as applied to claims 1, 2, 5 and 6 above, and further in view of Zou et al. (2002, J. Neuroscience, Vol. 22(12), pgs. 4833-4841) for reasons of record in the Non-Final office action mailed on 12/29/2008 and repeated below.

Woodbury and Guillemot combined teach a method of using bHLH transcription factors to transdifferentiate MSC. Woodbury and Guillemot do not teach culturing MSC in medium supplemented with N2.

However at the time of filing it was known in to be routine in the art to use N2 supplement when culturing neuronal cells. Zou et al. teach a method of culturing cerebral cortical neuronal cells with N2 supplement (pg. 4834 col. 1 parag. 2). Zou continues to teach that they used N2 supplements because it inhibits neuronal death (pg. 4835 col. 2 parag. 2).

Thus it would have been prima facie obvious to the ordinary artisan at the time of filing to combine the teachings of Zou regarding using N2 supplement in culture media to prevent neuronal cell death with the teachings of Woodbury and Guillemot regarding a method of transdifferentiating MSC into neuronal cells to use N2 supplement in culture media to prevent the death of newly transdifferentiated neuronal cells.

Thus the cited art clearly provides a case of prima facie obviousness.

Response to Arguments

Applicants Arguments

Applicants argue that the rejection of claim 8 is traversed for the same reasons set forth in the rejection of claims 1, 2, 5 and 6. Applicants continue that further Zhou does not teach or suggest the method of claim 1 nor claims 2, 5, and 6 in combination with Woodbury and Guillemot. These arguments are not persuasive.

Response

As discussed above the rejection is maintained and further Applicant has not indicated any particular arguments or deficiencies in the Zhou reference concerning its use in the pending rejection.

Allowable Subject Matter

Claim 7 is objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

Claim 7 is free of the prior art.

Conclusion

No claims are allowed.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to David Montanari whose telephone number is (571)272-3108. The examiner can normally be reached on M-Tr 8-6.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Peter Paras can be reached on 1-571-272-4517. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

David A. Montanari

AU 1632

/Valarie Bertoglio/

Primary Examiner, Art Unit 1632